L16 ANSWER 106 OF 120 MEDLINE DUPLICATE 44

ACCESSION NUMBER: 89001165 MEDLINE
DOCUMENT NUMBER: 89001165 PubMed ID: 3262381
TITLE: Regulation of interleukin-6 expression in cultured human blood monocytes and monocyte-derived macrophages.
AUTHOR: Bauer J; Ganter U; Geiger T; Jacobshagen U; Hirano T; Matsuda T; Kishimoto T; Andus T; Acs G; Gerok W; +
CORPORATE SOURCE: Medizinische Klinik, Universitat Freiburg, FRG.
SOURCE: BLOOD, **(1988 Oct)** 72 (4) 1134-40.
Journal code: A8G; 7603509. ISSN: 0006-4971.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 198811
ENTRY DATE: Entered STN: 19900308
Last Updated on STN: 19970203
Entered Medline: 19881115

L19 ANSWER 47 OF 69 BIOSIS COPYRIGHT 2001 BIOSIS
ACCESSION NUMBER: 1991:478629 BIOSIS
DOCUMENT NUMBER: BA92:112389
TITLE: ENDOGENOUS INTERFERON SPECIFICALLY REGULATES NEWCASTLE DISEASE VIRUS-INDUCED CYTOKINE GENE EXPRESSION IN MOUSE MACROPHAGES.
AUTHOR(S): ZAWATZKY R; WURMBAECK H; FALK W; HOMFELD A
CORPORATE SOURCE: INSTITUT VIRUSFORSCHUNG, DEUTSCHES KREBSFORSCHUNGSZENTRUM, D-6900 HEIDELBERG, GERMANY.
SOURCE: J VIROL, (1991) 65 (9), 4839-4846.
CODEN: JOVIAM. ISSN: 0022-538X.
FILE SEGMENT: BA; OLD
LANGUAGE: English

AB In macrophages from inbred mice, the magnitude of the interferon (IFN) response to Newcastle disease virus (NDV) infection is under genetic control of the If-1 locus, which carries the allele for either high (h) or low (l) IFN production. Here, we report that the activity of genes within the If-1 locus is influenced by macrophage-derived endogenous IFN. In addition to various other biological effects, we observed that endogenous IFN specifically downregulated NDV-induced IFN and interleukin 6 production. Preculture of bone marrow-derived macrophages (BMM) from BALB/c (If-1l) mice in macrophage colony-stimulating factor plus anti-IFN-.beta. provoked a 30- to 50-fold increase in NDV-induced cytokine production compared with induced control cultures in macrophage colony-stimulating factor alone, whereas only a 4- to 6-fold increase was observed in anti-IFN-.beta.-treated BMM from C57BL/6 (If-1h) mice. This resulted in nearly complete abrogation of the genetically determined difference in the response to NDV. The increase was specific for NDV and was marked by strong additional activation of IFN-.alpha. genes. Studies using BMM from B6.C-H28c If-1l congenic mice gave results identical to those obtained with BALB/c BMM. Addition of 20 IU of recombinant IFN-.alpha.4 to anti IFN-.beta.-treated macrophages from B6.C-H28c mice 20 h prior to NDV infection strongly downregulated the IFN-.alpha., IFN-.beta., and interleukin 6 responses. The genetic difference between macrophages from If-1h and If-1l mice was thus reestablished, since the same treatment caused only weak reduction of NDV-induced cytokine gene expression in BMM from C57BL/6 mice. These data suggest that the If-1h and If-1l alleles harbor IFN-inducible genes that, following activation, specifically suppress subsequent cytokine gene expression in response to NDV.

L7 ANSWER 14 OF 16 MEDLINE DUPLICATE 13
ACCESSION NUMBER: 94086125 MEDLINE
DOCUMENT NUMBER: 94086125 PubMed ID: 8262648
TITLE: Necessity and sufficiency of **beta interferon** for **nitric oxide** production in mouse peritoneal macrophages.
AUTHOR: Zhang X; Alley E W; Russell S W; Morrison D C
CORPORATE SOURCE: Department of Microbiology, Molecular Genetics and Immunology, University of Kansas Medical Center, Kansas City 66160.
CONTRACT NUMBER: PO1-CA-54474 (NCI)
R37-A1-23447
SOURCE: INFECTION AND IMMUNITY, **(1994 Jan)** 62 (1) 33-40.
Journal code: GO7; 0246127. ISSN: 0019-9567.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199401
ENTRY DATE: Entered STN: 19940209
Last Updated on STN: 19940209
Entered Medline: 19940127

AB Bacterial lipopolysaccharide and some cytokines can activate macrophages to secrete **nitric oxide**. Macrophage-derived **nitric oxide** is a key cytotoxic factor for microbicidal and tumoricidal processes. We report here that a monoclonal antibody specific for **beta interferon** inhibited lipopolysaccharide-induced **nitric oxide** production in thioglycolate-elicited C3HeB/FeJ peritoneal macrophages and macrophage-like cell line RAW 264.7. In addition, exogenous added **beta interferon** enabled lipopolysaccharide-hyporesponsive thioglycolate-elicited C3H/HeJ peritoneal macrophages to produce **nitric oxide** in response to lipopolysaccharide. These data support the concept that **beta interferon** provides an essential signal(s) for lipopolysaccharide-triggered **nitric oxide** production by mouse macrophages. Heat-killed Staphylococcus aureus, a gram-positive bacterium which was unable to initiate **nitric oxide** production in thioglycolate-elicited C3HeB/FeJ peritoneal macrophages in vitro, promoted **nitric oxide** formation in the presence of **beta interferon**, suggesting that **beta interferon** may be a general cofactor necessary for bacterium-derived stimulus-induced **nitric oxide** production in these macrophages. However, neither **beta interferon** nor tumor necrosis factor alpha, alone or in combination, triggered **nitric oxide** production in thioglycolate-elicited mouse peritoneal macrophages, demonstrating that these macrophage-derived cytokines, while necessary, were not sufficient by themselves for the induction of **nitric oxide** production in these cells. On the other hand, gamma interferon and tumor necrosis factor alpha acted together to induce **nitric oxide** production in vitro in the absence of lipopolysaccharide in thioglycolate-elicited mouse peritoneal macrophages, indicating that these two types of interferons provided different signals during the activation of these macrophages.

L14 ANSWER 15 OF 29 MEDLINE
ACCESSION NUMBER: 87025824 MEDLINE
DOCUMENT NUMBER: 87025824 PubMed ID: 3533071
TITLE: Homogeneous **interferon-beta**-inducing 25K factor (IL-1 beta) has connective tissue cell stimulating activities.
AUTHOR: Bunning R A; Van Damme J; Richardson H J; Hughes D E; Opdenakker G; Billiau A; Russell R G
SOURCE: BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS, **(1986 Sep 30)** 139 (3) 1150-7.
Journal code: 9Y8; 0372516. ISSN: 0006-291X.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198611
ENTRY DATE: Entered STN: 19900302
Last Updated on STN: 20000303
Entered Medline: 19861107

AB The human **interferon-beta**-inducing 22K factor has been shown to have structural homologies with interleukin-1 beta (IL-1 beta) and some of the activities attributed to IL-1. We have shown that 22K factor, purified to homogeneity and endotoxin free, has connective tissue cell stimulating activities, indicating that these activities are due to a naturally occurring species of IL-1 beta and not contaminating factors. 22K factor stimulated the production of prostaglandin E, caseinase activity and plasminogen activator activity in human articular chondrocytes in culture. This cell system appears highly sensitive to 22K factor activity. 22K factor also stimulated the resorption of bovine nasal cartilage and neonatal mouse calvaria.

L

L14 ANSWER 22 OF 29 BIOSIS COPYRIGHT 2001 BIOSIS
ACCESSION NUMBER: 1988:433075 BIOSIS
DOCUMENT NUMBER: BR35:85205
TITLE: THE EFFECT OF HUMAN **INTERFERON-BETA** -INDUCING 22K FACTOR 22K ON HUMAN **BONE**-DERIVED OSTEOBLAST-LIKE CELLS.
AUTHOR(S): EVANS D B; BUNNING R A D; VAN DAMME J; RUSSELL R G G
CORPORATE SOURCE: DEP. HUMAN METABOLISM AND CLINICAL BIOCHEM., UNIV. SHEFFIELD MED. SCH., SHEFFIELD S10 2RX, UK.
SOURCE: SECOND INTERNATIONAL WORKSHOP ON CELLS AND CYTOKINES IN BONE AND CARTILAGE, DAVOS, SWITZERLAND, APRIL 9-12, 1988. CALCIF TISSUE INT, (1988) 42 (SUPPL), A17. CODEN: CTINDZ. ISSN: 0171-967X.
DOCUMENT TYPE: Conference
FILE SEGMENT: BR; OLD
LANGUAGE: English

L

L16 ANSWER 31 OF 120 BIOSIS COPYRIGHT 2001 BIOSIS
ACCESSION NUMBER: 1993:44954 BIOSIS
DOCUMENT NUMBER: PREV199344021804
TITLE: Effect of **interferon beta**-ser on **interleukin 6** production and on transcription of the nuclear factor IRF-1 in human myeloma cell lines.
AUTHOR(S): Humpe, A. (1); Kiss, T.; Trumper, L. H.; Messner, H. A.
CORPORATE SOURCE: (1) Dep. Med., Sect. Hematol. Oncol., Georg-August-University Goettingen, Robert-Koch-Str. 40, D-3400 Goettingen Germany
SOURCE: Annals of Hematology, (1992) Vol. 65, No. SUPPL., pp. A72.

Meeting Info.: Annual Congress of the German Society of Hematology and Oncology, Berlin, Germany, October 4-7, 1992. ANN HEMATOL
ISSN: 0939-5555.
DOCUMENT TYPE: Conference
LANGUAGE: English

L14 ANSWER 21 OF 29 BIOSIS COPYRIGHT 2001 BIOSIS
ACCESSION NUMBER: 1992:131514 BIOSIS
DOCUMENT NUMBER: BR42:59214
TITLE: INTRALESIONAL **BETA INTERFERON**-THERAPY FOR REFRACTORY METASTASIS FROM SOLID TUMORS.
AUTHOR(S): SCHNALKE D; WILDFANG I; EMMINGER A; SCHMOLL H J
CORPORATE SOURCE: DIV. RADIOTHERAPY, HANNOVER UNIV. MED. SCH.
SOURCE: ANNUAL GENERAL MEETING OF THE GERMAN AND AUSTRIAN SOCIETY FOR HEMATOLOGY AND ONCOLOGY, INNSBRUCK, AUSTRIA, OCTOBER 10-13, 1991. ONKOLOGIE, (1991) 14 (SUPPL 2), 147. CODEN: ONKOD2. ISSN: 0378-584X.
DOCUMENT TYPE: Conference
FILE SEGMENT: BR; OLD
LANGUAGE: English

L

L9 ANSWER 12 OF 16 MEDLINE
ACCESSION NUMBER: 90053674 MEDLINE
DOCUMENT NUMBER: 90053674 PubMed ID: 2683781
TITLE: Associations of the skeletal and immune systems.
AUTHOR: Hong R
CORPORATE SOURCE: Department of Pediatrics, University of Wisconsin Clinical Science Center, Madison 53792.
SOURCE: AMERICAN JOURNAL OF MEDICAL GENETICS, (1989 Sep) 34 (1) 55-9. Ref: 16
Journal code: 3L4; 7708900. ISSN: 0148-7299.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198911
ENTRY DATE: Entered STN: 19900328
Last Updated on STN: 19900328
Entered Medline: 19891127

AB Certain disorders of the immune system seem to be associated with skeletal defects. The association was first recorded by McKusick et al. (Bulletin of the Johns Hopkins Hospital 116:285-326, 1964). A number of relationships between lymphocytes and osteocytes can be proposed. These include a common environment for development, common metabolic needs and effects upon osteocytes by products (cytokines) elaborated from lymphocytes or monocytes during immune responses. Thus, bony defects of varying degrees of severity are seen in short-limb dwarfs, cartilage-hair hypoplasia, and adenosine deaminase (ADA) deficiency. Cytokine activation of **osteoclasts** accounts for the lytic lesions seen in malignancies and the excessive bone resorption which accompanies **autoimmune** disorders such as rheumatoid arthritis. Correction of primary immune deficiency is accomplished by bone marrow transplantation. If the bony abnormality is subtle (as in some cases of ADA deficiency) the skeletal problem is resolved; if the bone defect is major as in short-limb dwarfism, no improvement is seen.

L9 ANSWER 13 OF 16 MEDLINE DUPLICATE 6

L7 ANSWER 8 OF 10 CANCERLIT
ACCESSION NUMBER: 92688064 CANCERLIT
DOCUMENT NUMBER: 92688064
TITLE: THE HYPERCALCEMIA OF CANCER. CLINICAL IMPLICATIONS AND PATHOGENIC MECHANISMS.
AUTHOR: Mundy G R; Ibbotson K J; D'Souza S M; Simpson E L; Jacobs J W; Martin T J
CORPORATE SOURCE: Dept. of Medicine, Univ. of Texas Health Science Center, San Antonio, TX.
SOURCE: N Engl J Med, (1984). Vol. 310, No. 26, pp. 1718-27. ISSN: 0028-4793.
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE) General Review; (REVIEW)
FILE SEGMENT: ICDB
LANGUAGE: English
ENTRY MONTH: 199211

AB Hypercalcemia (HyCal), one of the most common metabolic disorders accompanying neoplasia, with an estimated incidence of 150 new cases per million persons per year, can cause the patient (pt) great discomfort. When occurring in cancer pts, HyCal is usually progressive, and symptoms may begin at relatively low serum concentrations of calcium. Common symptoms include nausea, vomiting, anorexia, lethargy, confusion, stupor, and eventual coma. (Osteitis fibrosa cystica is a rare symptom.) Unfortunately, these symptoms can easily be confused with the end stages of malignant disease or with the effects of cytotoxic chemotherapy or radiation therapy. HyCal occurs most commonly with squamous carcinomas of the lung (but not with anaplastic or oat-cell lung tumors), breast cancer, cholangiocarcinomas and certain carcinomas induced by vasoactive intestinal peptide. HyCal occurs rarely, if ever, in **cancers** of the **colon** or uterine cervix. Bone histologic studies of HyCal occurring in hematologic cancers (myeloma, lymphosarcoma, Burkitt's lymphoma, adult T-cell leukemia) show an increase in osteoclastic bone resorption adjacent to neoplastic cells. Bone radiologic studies in such cases show a preponderance of osteolytic lesions with occasional diffuse osteopenia. Factors implicated as causative in such cases include **osteoclast**-activating factor and 1,25-dihydroxyvitamin D. Bone histologic studies of solid tumors with bone metastases (breast, lung, pancreatic) show a variable osteoblastic response in addition to an increase in local osteoclastic bone resorption. Bone radiologic studies in such cases typically show discrete lytic lesions and a variable sclerotic response. Factors implicated in the induction of HyCal in such cases include prostaglandins and direct erosion by tumor cells. Bone histologic studies in cases of HyCal occurring in pts with solid tumors without metastases (lung, kidney, pancreatic, ovarian) not only show increased osteoclastic bone resorption, but also decreased bone formation. No abnormalities are normally noted in such cases in bone radiologic studies. However, there may be an increase in fractional excretion of phosphate, an increase in nephrogenic cyclic AMP, and/or a decrease in immunoreactive parathyroid hormone. Factors implicated in the etiology of HyCal in pts with such tumors include parathyroid hormone, prostaglandins, transforming growth factors, factors that interact with PTH receptor, and colony-stimulating activity. HyCal results from tumor-stimulated

osteoclastic bone resorption. In addition to the induction of HyCal, such bone resorption also induces osteolytic bone metastasis which is associated with even more morbidity and mortality than is HyCal. (114 Refs)

L23 ANSWER 8 OF 196 MEDLINE DUPLICATE 7
ACCESSION NUMBER: 96082342 MEDLINE
DOCUMENT NUMBER: 96082342
TITLE: Nitric oxide: a cytokine-induced regulator of bone resorption.
AUTHOR: Ralston S H; Ho L P; Helfrich M H; Grabowski P S; Johnston P W; Benjamin N
CORPORATE SOURCE: Department of Medicine & Therapeutics, University of Aberdeen Medical School, Foresterhill, U.K.
SOURCE: JOURNAL OF BONE AND MINERAL RESEARCH, **(1995 Jul)** 10 (7) 1040-9.
Journal code: 130. ISSN: 0884-0431.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199602

AB Nitric oxide (NO) has been reported to inhibit **osteoclastic** bone resorption, yet potent stimulators of bone resorption, such as interleukin-1 (IL-1) and tumor necrosis factor (TNF), are known to stimulate NO production. This paradox prompted us to reinvestigate the relationship between NO production and bone resorption in mouse calvarial organ cultures. Control cultures and those stimulated with calciotropic hormones and individual cytokines produced little NO, and under these conditions the NO synthase inhibitor, L-NG-monomethyl arginine (LMMA), had no significant effect on bone resorption. Cytokine combinations were much more potent stimulators of NO production than individual cytokines. Dramatic stimulation of NO production and inhibition of bone resorption resulted when **gamma-interferon** (IFN) was combined with IL-1 or TNF and these effects were reversed by LMMA. IFN had no effect on bone resorption and little effect on NO production when used alone or in combination with calciotropic hormones, however, suggesting that IFN selectively inhibits cytokine-induced bone resorption by generating large amounts of NO. IL-1 and TNF acted together to stimulate NO production but to a lesser degree than when combined with IFN. LMMA inhibited bone resorption induced by IL-1 and TNF, suggesting that lower concentrations of NO stimulate bone resorption. Experiments with the pharmacological NO donor S-nitroso-acetyl-penicillamine (SNAP) supported this view in showing generalized suppression of bone resorption at high SNAP concentrations, but potentiation of IL-1 induced bone resorption at lower SNAP concentrations. We conclude that cytokines are potent inducers of NO in bone and that cytokine-induced NO production has biphasic effects on bone resorption. (ABSTRACT TRUNCATED AT 250 WORDS)

L23 ANSWER 38 OF 196 MEDLINE DUPLICATE 19
ACCESSION NUMBER: 94283276 MEDLINE
DOCUMENT NUMBER: 94283276
TITLE: Human **osteoblast**-like cells produce nitric oxide and express inducible nitric oxide synthase.
AUTHOR: Ralston S H; Todd D; Helfrich M; Benjamin N; Grabowski P S
CORPORATE SOURCE: Department of Medicine and Therapeutics, University of Aberdeen Medical School, Foresterhill, United Kingdom.
SOURCE: ENDOCRINOLOGY, **(1994 Jul)** 135 (1) 330-6.
Journal code: EGZ. ISSN: 0013-7227.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals; Cancer Journals
ENTRY MONTH: 199409

AB Nitric oxide (NO) is a short-lived free radical that plays an important regulatory role in several biological processes. Cytokines such as interleukin-1, tumor necrosis factor, and **interferon-gamma** have been shown to stimulate NO production in many cells types. Although these cytokines are known to have potent effects on bone remodeling and **osteoblast** function, the role of NO as an effector molecule in bone has been little studied. Here we investigate the effects of cytokines and calciotropic hormones on NO production by human **osteoblast**-like cells (hOB) and the role of NO as a modulator of **osteoblast** growth. Unstimulated hOB produced little NO, as reflected by measurement of nitrite concentrations in hOB-conditioned medium. NO production was not significantly altered by PTH and 1,25-dihydroxyvitamin D or human recombinant interleukin-1 beta (10 U/ml), tumor necrosis factor-alpha (25 ng/ml), and **interferon-gamma** (100 U/ml) individually. Combinations of all three cytokines at these concentrations, however, dramatically increased both NO generation and cGMP production. The stimulatory effect of cytokines on NO production began 12 h after exposure and was inhibited by cycloheximide, actinomycin-D, dexamethasone, and the competitive inhibitor of NO synthase L-NG-monomethylarginine. Reverse transcription/polymerase chain reaction analysis of hOB RNA, followed by direct sequencing of the amplified products, showed that hOB express the inducible, rather than the endothelial or neuronal, forms of NO synthase. Cytokine-induced increases in NO production were associated with a marked inhibition of [3H]thymidine uptake to less than 10% of that observed in control cultures. Abrogation of NO synthesis with L-NG-monomethylarginine under these conditions significantly increased [3H]thymidine uptake to approximately 20% of the control value, suggesting that NO may partly be responsible for the inhibition of **osteoblast** proliferation induced by these cytokines. Our data indicate that proinflammatory cytokines induce NO production in **osteoblast**-like cells and show and that this mediator plays a role in regulating cell growth. These findings may have important implications for the pathogenesis and management of bone loss in diseases associated with cytokine activation, such as rheumatoid arthritis.

L23 ANSWER 65 OF 196 MEDLINE
ACCESSION NUMBER: 93365182 MEDLINE
DOCUMENT NUMBER: 93365182
TITLE: **Osteopetrosis**. The pharmaco-physiologic basis of therapy.
AUTHOR: Key L L Jr; Ries W L
CORPORATE SOURCE: Department of Pediatrics, Brenner Children's Hospital, Bowman Gray School of Medicine, Wake Forest University, Winston-Salem, North Carolina..
SOURCE: CLINICAL ORTHOPAEDICS AND RELATED RESEARCH, **(1993 Sep)** (294) 85-9.
Journal code: DFY. ISSN: 0009-921X.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 199312

AB Medical treatments of **osteopetrosis** have attempted to improve hematologic function, reduce the **osteosclerotic** condition, and/or improve immune function. Prednisone therapy has improved hematologic function in some patients, but has not resulted in a reduction in bone mass. Calcium deficient diets have limited further sclerosis in some patients. High-dose calcitriol and parathormone infusions have stimulated **osteoclastic** activity. In some patients, high-dose calcitriol has resulted in clinical improvement. Newer treatments, such as **interferon gamma** and macrophage colony stimulating factor, may alter the **osteoclastic** and immune defects by stimulating cellular formation and function. These therapies, alone or in combination, ameliorate but do not cure the **osteopetrotic** condition.

L19 ANSWER 48 OF 89 MEDLINE
ACCESSION NUMBER: 97006224 MEDLINE
DOCUMENT NUMBER: 97006224
TITLE: Bone remodeling, normal and abnormal: a biological basis for the understanding of cancer-related bone disease and its treatment.
AUTHOR: Parfitt A M
SOURCE: CANADIAN JOURNAL OF ONCOLOGY, (1995 Dec) 5 Suppl 1 1-10. Ref: 50
Journal code: B01. ISSN: 1183-2509.
PUB. COUNTRY: Canada
Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199702
ENTRY WEEK: 19970204

AB Remodeling the cyclical replacement of old bone by new, serves to maintain its mechanical and metabolic functions. In each cycle a circumscribed volume of bone is removed by osteoclastic resorption and subsequently replaced by osteoblastic formation at the same location. Remodeling is carried out by elongated structures known as basic multicellular units (BMU) that travel through or across the surface of bone. Each BMU lasts about six months, with continued sequential recruitment of new **osteoclasts** and osteoblasts. Abnormal bone remodeling involves some combination of loss of directional control, **increase** in number of remodeling cycles and incomplete replacement. In **metastatic** bone disease, tumor cells find the hematopoietic bone marrow conducive to their survival and growth, because they can manipulate the local cytokine network to **increase** recruitment of **osteoclasts** from local precursors and so **increase** bone resorption. The effect on bone formation is biphasic; an initial **increase** is due partly to the normal evolution of the BMU, and partly to the induction of reparative woven bone formation. Later, normal BMU-based bone formation may fall to subnormal levels. In some tumors, a generalized **increase** in **osteoclast** recruitment and decline in bone formation are the systemic responses to one or more agents released by tumor cells into the circulation, of which the most frequent is parathyroid hormone-related peptide, but in both **metastatic** and non-**metastatic** disease, the cellular events in bone are essentially the same. Cancer-related bone disease is amenable to treatment with drugs that inhibit **osteoclast** recruitment, of which the bisphosphonates are the most effective. Treatment should be started before there has been irreparable damage to bone structure and before the onset of hypercalcemia. Although bisphosphonates remain in bone for a long time, adverse effects are very unlikely within the patient's lifetime.

L

L23 ANSWER 7 OF 196 MEDLINE DUPLICATE 6
ACCESSION NUMBER: 95272641 MEDLINE
DOCUMENT NUMBER: 95272641
TITLE: Long-term treatment of **osteopetrosis** with recombinant human **interferon gamma** [see comments].
COMMENT: Comment in: N Engl J Med 1995 Jun 15;332(24):1639-40
AUTHOR: Key L L Jr; Rodriguiz R M; Willi S M; Wright N M; Hatcher H
C; Eyre D R; Cure J K; Griffin P P; Ries W L
CORPORATE SOURCE: Department of Pediatric Endocrinology, Medical University of South Carolina, Charleston, USA..
CONTRACT NUMBER: FDR-000768 (NCRR)
M01-RR-01070
SOURCE: NEW ENGLAND JOURNAL OF MEDICINE, **(1995 Jun 15)** 332 (24) 1594-9.
Journal code: NOW. ISSN: 0028-4793.
PUB. COUNTRY: United States
(CLINICAL TRIAL)
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals; Cancer Journals
ENTRY MONTH: 199508

AB BACKGROUND. Congenital **osteopetrosis** is a rare **osteosclerotic** bone disease characterized by both a defect in **osteoclastic** function and reduced generation of superoxide by leukocytes. The disease is frequently fatal during the first decade of life. A six-month trial of therapy with recombinant human **interferon gamma**-1b in eight patients with **osteopetrosis** provided evidence of benefit, prompting this study of more prolonged therapy. METHODS. We studied 14 patients with severe **osteopetrosis** treated with subcutaneous injections of recombinant human **interferon gamma**-1b (1.5 micrograms per kilogram of body weight per dose) three times per week for at least 6 months; 11 patients were treated for 18 months. We assessed the effect of therapy by evaluating the patients' clinical status, measuring blood counts and biochemical markers of bone turnover, and performing bone marrow imaging and bone biopsies. RESULTS. After 6 months of therapy, all 14 patients had decreases in trabecular-bone area (determined by histomorphometric analysis of bone-biopsy specimens) and increases in bone marrow space (determined by marrow imaging), and the improvement was sustained in the 11 patients treated for 18 months. The mean (+SD) hemoglobin concentration increased from 7.5 +/- 2.9 to 10.5 +/- 0.3 g per deciliter ($P = 0.05$), and superoxide generation by granulocyte-macrophage colonies increased ($P < 0.001$) after 18 months of therapy. In six patients for whom pretreatment data were available, there was a 96 percent decrease in the frequency of infections requiring antibiotic therapy during interferon treatment. There were no side effects necessitating the discontinuation of therapy. CONCLUSIONS. Long-term therapy with **interferon gamma** in patients with **osteopetrosis** increases bone resorption and hematopoiesis and improves leukocyte function.

L

L23 ANSWER 44 OF 196 MEDLINE DUPLICATE 22
ACCESSION NUMBER: 95007639 MEDLINE
DOCUMENT NUMBER: 95007639
TITLE: Comparative study of inhibitory effects by murine **interferon gamma** and a new bisphosphonate (alendronate) in hypercalcemic, nude mice bearing human tumor (LJC-1-JCK).
AUTHOR: Tohkin M; Kakudo S; Kasai H; Arita H
CORPORATE SOURCE: Shionogi Research Laboratories, Shionogi & Co. Ltd. Fukushima-ku Osaka, Japan.
SOURCE: CANCER IMMUNOLOGY, IMMUNOTHERAPY, **(1994 Sep)** 39 (3) 155-60.
Journal code: CN3. ISSN: 0340-7004.
PUB. COUNTRY: GERMANY: Germany, Federal Republic of
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals; Cancer Journals
ENTRY MONTH: 199501

AB The inhibitory effect of murine **interferon gamma** (muIFN gamma) on humoral hypercalcemia in nude mice bearing lower-jaw cancer (LJC-1-JCK), in which parathyroid-hormone(PTH)-related protein is responsible for causing humoral hypercalcemia by activating bone resorption, was examined in comparison with that of a new bisphosphonate, 4-amino-1-hydroxybutylidene-1,1-bisphosphonate (alendronate). muIFN gamma was injected into tumor-bearing nude mice for 5 days before the establishment of hypercalcemia. The increase of plasma calcium concentration was delayed and this effect continued for more than 6 days even after the injection was stopped. Alendronate markedly suppressed hypercalcemia in tumor-bearing nude mice but this inhibitory effect continued for less than 6 days. Neither muIFN gamma nor alendronate affected the tumor volume or serum PTH-related protein concentration. Injection of muIFN gamma into mice for 3 days almost completely abolished the formation of multinucleated **osteoclast**-like cells from bone marrow cells in vitro, whereas injection of alendronate into mice had no effect. These findings suggested that muIFN gamma suppressed the formation of **osteoclasts**, resulting in the prolonged decrease of plasma calcium concentration in hypercalcemic tumor-bearing nude mice, whereas alendronate is cytotoxic to functionally mature **osteoclasts** and inhibited **osteoclastic** bone resorption, resulting in a marked decrease in the plasma calcium concentration in tumor-bearing

L19 ANSWER 67 OF 89 MEDLINE
ACCESSION NUMBER: 90358545 MEDLINE
DOCUMENT NUMBER: 90358545
TITLE: Palliative therapy in cancer. 4. Palliation of the symptoms
from a malignant tumor. (2).
AUTHOR: Urushizaki I
CORPORATE SOURCE: Sapporo Medical College, East Sapporo Hospital..
SOURCE: GAN TO KAGAKU RYOHO [JAPANESE JOURNAL OF CANCER AND CHEMOTHERAPY], (1990 Aug) 17 (8 Pt 1) 1525-35. Ref: 32
Journal code: 6T8. ISSN: 0385-0684.
PUB. COUNTRY: Japan
Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: Japanese
FILE SEGMENT: Priority Journals; Cancer Journals
ENTRY MONTH: 199011

AB Patients suffering from malignant disease will probably develop some metabolic abnormality of electrolytes. Hypernatremia is defined as an elevation of serum natrium over 150 mEq/l and caused by decrease of water intake, low level of ADH secretion and impaired response of kidney to ADH.

Hyponatremia below 135 mEq/l of serum natrium is caused by SI-DAH, sick cell syndrome and increased loss of natrium from the kidney. On the other hand, hyperkalemia is defined as an elevation of serum kalium over 5.0 mEq/l and caused by acute tumor cell lysis syndrome, adrenal and renal insufficiency. Hypokalemia is caused by kalium loss from kidney and hypersecretion of mineral corticoid. Hypercalcemia is found in the high frequency among patients with malignant disease. Hypercalcemia is defined as an elevation of serum calcium over 11.0 mg/dl, although the most important aspect is the level of ionized calcium. The excess calcium causes defective urinary concentration with polydipsia, nausea and vomiting leading to volume depletion. At serum calcium levels about 13.8 mg/dl, there may be rapid deterioration or renal function, dehydration, coma and cardiac arrhythmias. Hypercalcemia is rarely the first manifestation of cancer. There are three principle pathogenic causes of malignant hypercalcemia, 1) hypercalcemia is a feature of several hematological cancers, including Burkitt's lymphoma, T cell leukemia, but most commonly with myeloma. The hypercalcemia in these myeloma patients is due to the secretion of an **osteoclast** activator, a lymphokine by the myeloma cells. 2) all patients with bony **metastases** have biochemical evidence of increased bone resorption. However, not all patients with bony **metastases** develop hypercalcemia. Probably the hypercalcemia is due partially to increased renal tubular reabsorption of calcium, mediated by a humoral factor, with activity similar to that of parathormone. 3) hypercalcemia in the patients without bony **metastases** is due to increased bone resorption caused by the ectopic secretion by the tumor. Mildly symptomatic patients will benefit from modest salt loading. They are dehydrated and replacement of the extracellular fluid is the first line of treatment. This may require 4-10 l normal saline/24 h. In addition, frusemide will **increase** calcium excretion. Calcitonin may be given subcutaneously or intravenously to refuse the mobilisation of calcium from bone. Glucocorticoids are

unhelpful, but will prolong the effect of calcitonin. A diphosphonate is also useful.

L19 ANSWER 60 OF 89 MEDLINE DUPLICATE 25
ACCESSION NUMBER: 91187906 MEDLINE
DOCUMENT NUMBER: 91187906
TITLE: Osteoclastic inhibition: an action of nitric oxide not mediated by cyclic GMP.
AUTHOR: MacIntyre I; Zaidi M; Alam A S; Datta H K; Moonga B S; Lidbury P S; Hecker M; Vane J R
CORPORATE SOURCE: Department of Medicine and Chemical Pathology, Royal Postgraduate Medical School, London, United Kingdom.
SOURCE: PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, (1991 Apr 1) 88 (7) 2936-40. Journal code: PV3. ISSN: 0027-8424.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals; Cancer Journals
ENTRY MONTH: 199107

AB The **osteoclast** is unique in its ability to resorb bone, and excessive osteoclastic activity has been implicated in osteoporosis, Paget disease of bone, rheumatoid arthritis, and the growth of **metastases** in bone. The activity of this cell is controlled by the main circulating inhibitor, calcitonin, in association with locally produced modulators. We show that nitric oxide (NO) may be an important member of the latter group. NO is produced by the vascular endothelium and nervous system and is involved in both neurotransmission and the regulation of blood pressure. However, our results show that the autocoid is also a potent inhibitor of **osteoclast** function. NO (30 microM) produced a decrease to approximately 50% of the original **osteoclast** spread area. Similar effects were also produced by 3-morpholinosydnonimine or sodium nitroprusside, reagents that spontaneously release NO. These shape changes were associated with a reduction of bone resorption after a 24-hr incubation of isolated **osteoclasts** on devitalized bone slices. NO is thought to act by stimulating guanylate cyclase, with a consequent **increase** in cyclic GMP, but a different mode of action is likely in the **osteoclast** since dibutyryl or 8-bromo cyclic GMP have no effect. It should be noted that calcitonin can produce similar changes in shape and activity but is associated with an **increase** in **osteoclast** intracellular calcium and cessation of membrane movement; neither of these is produced by NO, suggesting that its mode of action is different. The abundance of NO-producing endothelial cells in bone marrow and their proximity to **osteoclasts** suggests that marrow endothelial cells may play a physiological role in the regulation of osteoclastic activity.

L23 ANSWER 80 OF 196 BIOSIS COPYRIGHT 2000 BIOSIS

ACCESSION NUMBER: 1993:240576 BIOSIS
DOCUMENT NUMBER: PREV199344113776
TITLE: Recombinant human **interferon gamma** treatment of **osteoporosis**.
AUTHOR(S): Key, L. Lyndon, Jr.; Ries, William L.; Rodriguiz, Ramona M.; Wolf, William C.; Griffin, Paul
CORPORATE SOURCE: Dep. Pediatr., Div. Endocrinol. Orthop., Med. Univ. S.C., 171 Ashley Ave., Charleston, SC 29425 USA
SOURCE: Cohn, D. V. [Editor]; Gennari, C. [Editor]; Tashjian, A. H., Jr. [Editor]. International Congress Series, (1992) No. 1003, pp. 431-436. International Congress Series; Calcium regulating hormones and bone metabolism: Basic and clinical aspects, Vol. 11.
Publisher: Excerpta Medica 305 Keizersgracht, PO Box 1126, Amsterdam, Netherlands.
Meeting Info.: 11th International Conference on Calcium Regulating Hormones Florence, Italy April 24-29, 1992
ISSN: 0531-5131. ISBN: 0-444-89489-6.
DOCUMENT TYPE: Article
LANGUAGE: English

L27 ANSWER 2 OF 3 MEDLINE DUPLICATE 1
ACCESSION NUMBER: 90342617 MEDLINE
DOCUMENT NUMBER: 90342617
TITLE: Recombinant murine **interferon-gamma** inhibits the fusion of mouse **alveolar** macrophages in vitro but stimulates the formation of osteoclastlike cells on implanted syngeneic bone particles in mice in vivo.
AUTHOR: Vignery A; Niven-Fairchild T; Shepard M H
CORPORATE SOURCE: Department of Orthopedics, Yale University School of Medicine, New Haven, CT.
CONTRACT NUMBER: RO1-AM35004 (NIADDK)
K04-AR01694 (NIAMS)
SOURCE: JOURNAL OF BONE AND MINERAL RESEARCH, (1990 Jun) 5 (6) 637-44.
Journal code: 130. ISSN: 0884-0431.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199011

AB **Osteoclasts** are multinucleated cells that originate from the fusion of mononuclear precursors and are responsible for bone resorption. Indirect evidence from in vitro studies suggests that IFN-gamma and TNF-alpha inhibit and stimulate bone resorption, respectively, but contradictory results have emerged from the literature regarding the effects of IFN-gamma on macrophage multinucleation. Using highly sensitive model systems, the present work demonstrates that, in mice, rMuIFN-gamma inhibits the fusion of **alveolar** macrophages in vitro but augments the number of osteoclastlike cells on implanted syngeneic bone particles in vivo. Although rMuTNF-alpha fails to stimulate macrophage multinucleation in either system, treatment of implanted animals with rMuIFN-gamma appears to limit the inflammatory reaction and favor tissue repair.

L23 ANSWER 11 OF 196 BIOSIS COPYRIGHT 2000 BIOSIS
ACCESSION NUMBER: 1996:97924 BIOSIS
DOCUMENT NUMBER: PREV199698670059
TITLE: Cytokine-induced apoptosis in **osteoblast** cultures mediated by nitric oxide.
AUTHOR(S): Hughes, F. J. (1); Ghazi, R. (1); Hukkanen, M.; Buttery, L.; Polak, J.
CORPORATE SOURCE: (1) Dep. Periodontology, London Hosp. Med. Coll., London E1
2AD UK
SOURCE: Bone (New York), (1995) Vol. 17, No. 6, pp. 565.
Meeting Info.: Sixth Workshop on Cells and Cytokines in Bone and Cartilage Davos, Switzerland January 7-10, 1996
ISSN: 8756-3282.
DOCUMENT TYPE: Conference
LANGUAGE: English

L23 ANSWER 15 OF 196 BIOSIS COPYRIGHT 2000 BIOSIS
ACCESSION NUMBER: 1995:521720 BIOSIS
DOCUMENT NUMBER: PREV199598536020
TITLE: Enhanced expression of **interferon-gamma** (IFN-gamma) and **interferon-gamma** receptor (IFN-gamma-R) in synovium of patients with rheumatoid arthritis (RA) compared with synovium of patients with **osteoarthritis** (OA.
AUTHOR(S): Dolhain, R. J. E. M. (1); Ter Haar, N. T.; Hoefakker, S.; Tak, P. P. (1); De Leij, M.; Claassen, E.; Breedveld, F. C.
(1); Miltenburg, A. M. M. (1)
CORPORATE SOURCE: (1) Dep. Rheumatol., Univ. Hosp., Leiden Netherlands
SOURCE: Arthritis & Rheumatism, (1995) Vol. 38, No. 9 SUPPL., pp. S355.
Meeting Info.: 59th National Scientific Meeting of the American College of Rheumatology and the 30th National Scientific Meeting of the Association of Rheumatology Health Professionals San Francisco, California, USA October
21-26, 1995
ISSN: 0004-3591.
DOCUMENT TYPE: Conference
L

L23 ANSWER 28 OF 196 BIOSIS COPYRIGHT 2000 BIOSIS
ACCESSION NUMBER: 1994:221502 BIOSIS
DOCUMENT NUMBER: PREV199497234502
TITLE: Inducible production of nitric oxide in **osteoblast**-like cells and in fetal mouse bone explants is associated with suppression of **osteoclastic** bone resorption.
AUTHOR(S): Lowik, Clemens W. G. M. (1); Nibbering, Peter H.; Van De Ruit, Marjan; Papapoulos, Socrates E.
CORPORATE SOURCE: (1) Dep. Endocrinol., Univ. Hosp., Bldg. 1, C4-R89, Rijnsburgerweg 10, 2333 AA Leiden Netherlands
SOURCE: Journal of Clinical Investigation, (1994) Vol. 93, No. 4, pp. 1465-1472.
ISSN: 0021-9738.
DOCUMENT TYPE: Article
LANGUAGE: English

AB Nitric oxide (NO) has been suggested to be involved in the regulation of **osteoclast** activity. Since **osteoblasts**, through the release of various factors, are the main regulators of **osteoclastic** resorption, first we have investigated whether **osteoblast**-like cells and fetal mouse long bone explants are able to produce NO. Second, we have assessed the effect of NO on **osteoclastic** resorption in whole bone cultures. In this study we show that primary rat **osteoblast**-like cells as well as the clonal rat **osteoblast**-like cell line UMR-106, stimulated with IFN-gamma together with TNF-alpha and LPS, produce NO, measured as nitrite production. IL-1-alpha enhanced while TGF-beta-2 inhibited TNF-alpha + IFN-gamma + LPS-stimulated NO production in UMR-106 cells dose dependently. Both the cytokines, however, had no effect when given alone. The competitive inhibitor of NO production, N-G-monomethyl-arginine (L-NMMA), and cycloheximide abolished the increase in nitrite production induced by TNF-alpha + IFN-gamma + LPS, while hydrocortisone had no effect, as previously reported for chondrocytes. Calciotropic hormones had either no effect (1,25(OH)-2D-3) or had a small inhibitory effect (parathyroid hormone) on stimulated NO production. Furthermore, we found that in cultured fetal mouse long bone explants the combination of TNF-alpha + IFN-gamma + LPS as well as the NO donor sodium nitroprusside could inhibit **osteoclastic** resorption, measured as 45Ca release. The inhibition of resorption was prevented by concurrent administration of L-NMMA. Histological evaluation revealed that the TNF-alpha + IFN-gamma + LPS-induced inhibition of 45Ca release was associated with a decrease in the number of tartrate-resistant acid phosphatase-positive **osteoclasts**. We propose that the NO production by **osteogenic** cells (**osteoblasts** and chondrocytes) may represent an important regulatory mechanism of **osteoclastic** activity especially under pathological conditions characterized by release of bone-resorbing inflammatory cytokines.

SWER 30 OF 196 MEDLINE DUPLICATE 16
ACCESSION NUMBER: 94349860 MEDLINE
DOCUMENT NUMBER: 94349860
TITLE: **Interferon-gamma** causes loss of bone volume in vivo and fails to ameliorate cyclosporin A-induced **osteopenia**.
AUTHOR: Mann G N; Jacobs T W; Buchinsky F J; Armstrong E C; Li M; Ke H Z; Ma Y F; Jee W S; Epstein S
CORPORATE SOURCE: Division of Endocrinology and Metabolism, Albert Einstein Medical Center, Philadelphia, Pennsylvania 19141..
SOURCE: ENDOCRINOLOGY, **(1994 Sep)** 135 (3) 1077-83.
Journal code: EGZ. ISSN: 0013-7227.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals; Cancer Journals
ENTRY MONTH: 199412

AB **Interferon-gamma** (IFN gamma) in vitro inhibits both bone resorption and bone formation, resulting in a net decrease in bone turnover. In vivo administration of cyclosporin A (CsA) produces accelerated bone remodeling with resultant bone loss. The aim of this study was to investigate whether administration of IFN gamma to rats would favorably modify the high turnover **osteopenia** caused by CsA. Thirty-six male Sprague-Dawley rats were randomized into 4 equal groups to receive either CsA (15 mg/kg.day) or vehicle by gavage and IFN gamma (10(6) IU/kg.day) or vehicle by ip injection for 8 days. Group 1 received CsA vehicle plus IFN gamma vehicle; group 2 received CsA plus IFN gamma vehicle; group 3 received CsA vehicle plus IFN-gamma; group 4 received CsA plus IFN gamma. Blood was sampled on days 0, 4, and 8 for measurement of ionized calcium (Ca2+), PTH, 1,25-dihydroxyvitamin D, and bone gla protein. Tibiae were removed on day 8 after double tetracycline labeling for histomorphometric analysis. Ca2+ and PTH levels were similar in all groups during the study period. Rats receiving CsA (groups 2 and 4) had elevated levels of 1,25-dihydroxyvitamin D and bone gla protein, whereas rats receiving IFN gamma alone (group 3) had no change in levels of these parameters. Bone histomorphometry revealed that treatment with CsA and/or IFN gamma (groups 2-4) caused an increase in bone resorption surface and a decrease in some parameters of bone formation, resulting in a net loss of bone volume. Thus, IFN gamma failed to influence the **osteopenia** caused by CsA and on its own had adverse effects on bone in vivo. These results demonstrate that immune-mediating agents have opposing actions in vitro as compared to in vivo.

L23 ANSWER 36 OF 196 MEDLINE
ACCESSION NUMBER: 95098500 MEDLINE
DOCUMENT NUMBER: 95098500
TITLE: Regulation of bone metabolism by the kallikrein-kinin system, the coagulation cascade, and the acute-phase reactants.
AUTHOR: Lerner U H
CORPORATE SOURCE: Department of Oral Cell Biology, University of Umea, Sweden..
SOURCE: ORAL SURGERY, ORAL MEDICINE, AND ORAL PATHOLOGY, **(1994 Oct)** 78 (4) 481-93. Ref: 87
Journal code: OJU. ISSN: 0030-4220.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals; Dental Journals
ENTRY MONTH: 199503

AB Inflammation-induced localized bone resorption in diseases such as marginal and apical periodontitis, rheumatoid arthritis, and **osteomyelitis** is due to activation and recruitment of **osteoclasts** by locally produced cytokines and inflammatory mediators. Thus several interleukins (1, 3, 4, 6, and 11), tumor necrosis factors (alpha, beta), colony-stimulating factors (M and GM), leukemia inhibitory factor, **gamma-interferon**, and transforming growth factor-beta have effects on bone resorption and bone formation in vivo and in vitro. The kallikrein-kinin system and the coagulation cascade are also activated in inflammation. We have found that peptides produced in the kallikrein-kinin system (bradykinin, kallidin) and thrombin, the end product in the coagulation cascade, can stimulate bone resorption in vitro. The stimulatory effect of bradykinin is linked both to B1 and B2 bradykinin receptors. Both kinins and thrombin stimulate prostaglandin biosynthesis in bone parallel with the bone resorptive effect. The stimulatory effect of bradykinin on bone resorption is completely lost when the prostaglandin response is abolished, whereas thrombin can stimulate bone resorption both via prostaglandin-dependent and independent mechanisms. In addition, bradykinin and thrombin act in concert with interleukin-1 to synergistically stimulate bone resorption and prostaglandin biosynthesis. We also have found that one of the acute-phase reactants, haptoglobin, can stimulate bone resorption in vitro, indicating the possibility of generalized bone loss in chronic inflammatory diseases.

Moreover, haptoglobin synergistically potentiates bradykinin-induced and thrombin-induced prostanoid biosynthesis in **osteoblasts**. These observations indicate that the rate of bone resorption in inflammation-induced bone loss may not be due to a single factor but to the concerted action of several local or systemic factors.

L23 ANSWER 4 OF 196 MEDLINE DUPLICATE 4
ACCESSION NUMBER: 95269675 MEDLINE
DOCUMENT NUMBER: 95269675
TITLE: Interleukin 4, **interferon-gamma**, and prostaglandin E impact the **osteoclastic** cell-forming potential of murine bone marrow macrophages.
AUTHOR: Lacey D L; Erdmann J M; Teitelbaum S L; Tan H L; Ohara J; Shioi A
CORPORATE SOURCE: Department of Pathology, Jewish Hospital, Washington University, St. Louis, Missouri 63110, USA.
CONTRACT NUMBER: AR-42356 (NIAMS)
DE-05413 (NIDCR)
AR-32788 (NIAMS)
SOURCE: ENDOCRINOLOGY, **(1995 Jun)** 136 (6) 2367-76.
Journal code: EGZ. ISSN: 0013-7227.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals; Cancer Journals
ENTRY MONTH: 199508

AB Interleukin 4 (IL-4) is an immune cytokine that inhibits bone resorption in mice and suppresses **osteoclastic** cell formation in vitro through an undefined mechanism. In this report, we have established the cellular identity of the IL-4 target cell using a variety of bone marrow/stromal cell coculture methods. Initially, we found that the majority of IL-4's inhibition of **osteoclastic** cell formation was due to its effect on bone marrow cells, not stromal cells. Consequently, bone marrow macrophages were used as **osteoclastic** cell progenitors after they had been transiently exposed to IL-4 (48 h), before the addition of stromal cells, 1,25-dihydroxyvitamin D3, and dexamethasone. In this circumstance, IL-4 impaired subsequent **osteoclastic** cell formation, suggesting that the macrophage may be potentially targeted by many factors known to influence **osteoclast** formation. Consequently, we discovered that **interferon-gamma** (IFN gamma), prostaglandin E (PGE), and cell-permeant cAMP analogs also impacted **osteoclastic** cell formation when used to selectively treat bone marrow macrophages. IFN gamma suppressed **osteoclastic** cell formation, whereas PGE and cAMP analog treatment led to the formation of significantly enlarged **osteoclastic** cells. Importantly, PGE antagonized the inhibitory effects of both IL-4 and IFN gamma on the **osteoclastic** cell-forming potential of bone marrow macrophages. Collectively, these findings establish bone marrow macrophages as **osteoclastic** cell precursors with the degree of their commitment to the **osteoclast** pathway sensitive to the effects of soluble mediators, including IL-4, IFN gamma, and PGE.

L14 ANSWER 20 OF 29 BIOSIS COPYRIGHT 2001 BIOSIS
ACCESSION NUMBER: 1992:155092 BIOSIS
DOCUMENT NUMBER: BR42:71292
TITLE: POSTTRANSLATIONAL MODIFICATION OF TYPE I COLLAGEN INVOLVEMENT OF TGF-BETA.
AUTHOR(S): SEITZER U; BAETGE B; RAU C; BODO M; MUELLER P K
CORPORATE SOURCE: INST. MED. MOLEKULARBIOL., MED. UNIV. LUEBECK, RATZEBURGER ALLEE 160, W-2400 LUEBECK, GER.
SOURCE: FOURTH WORKSHOP ON CELLS AND CYTOKINES IN BONE AND CARTILAGE, DAVOS, SWITZERLAND, JANUARY 11-14, 1992. CALCIF TISSUE INT, (1992) 50 (SUPPL 1), A18.
CODEN: CTINDZ. ISSN: 0171-967X.
DOCUMENT TYPE: Conference
FILE SEGMENT: BR; OLD
LANGUAGE: English

L6 ANSWER 1 OF 2 BIOSIS COPYRIGHT 2001 BIOSIS
ACCESSION NUMBER: 1999:439767 BIOSIS
DOCUMENT NUMBER: PREV199900439767
TITLE: The therapeutic potential of IFNs-alpha/beta in rheumatoid arthritis.
AUTHOR(S): Fish, Eleanor (1); Wong, Thomas (1); Penninger, Josef (1); Keystone, Edward (1)
CORPORATE SOURCE: (1) University of Toronto, Toronto Canada
SOURCE: Journal of Interferon and Cytokine Research, (Sept., 1999) Vol. 19, No. SUPPL. 1, pp. S140.
Meeting Info.: Meeting of the International Society for Interferon and Cytokine Research with the participation of the European Cytokine Society Paris, France September 5-9, 1999 European Cytokine Society
. ISSN: 1079-9907.
DOCUMENT TYPE: Conference
LANGUAGE: English

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L14 ANSWER 1 OF 29 MEDLINE
ACCESSION NUMBER: 97026153 MEDLINE
DOCUMENT NUMBER: 97026153 PubMed ID: 8872332
TITLE: Tamoxifen and **interferon-beta** for the treatment of metastatic breast cancer.
AUTHOR: Repetto L; Giannessi P G; Campora E; Pronzato P; Vigani A; Naso C; Spinelli I; Conte P F; Rosso R
CORPORATE SOURCE: Department of Medical Oncology, Istituto Nazionale per la Ricerca sul Cancro, Genova, Italy.
SOURCE: BREAST CANCER RESEARCH AND TREATMENT, **(1996)** 39 (2) 235-8.
Journal code: A8X; 8111104. ISSN: 0167-6806.
PUB. COUNTRY: Netherlands
(CLINICAL TRIAL)
(CLINICAL TRIAL, PHASE II)
Journal; Article; (JOURNAL ARTICLE)
(MULTICENTER STUDY)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199701
ENTRY DATE: Entered STN: 19970128
Last Updated on STN: 19970128
Entered Medline: 19970102

AB It has been demonstrated, both in breast cancer cell lines and in metastatic breast cancer patients with cutaneous lesions that could be biopsied, that treatment with **interferon beta** (IFN-B) can increase expression of both estrogen (ER) and progesterone receptors (PgR). To evaluate the efficacy and toxicity of the combination of IFN and tamoxifen, 33 metastatic breast cancer patients were treated with the following regimen: IFN-B, 6.0 million units intramuscularly IU 3 times a week for two consecutive weeks followed by IFN-B 6.0 million IU im 3 times a week with concomitant tamoxifen 20 mg orally daily. Patients were pre and postmenopausal with median age of 60 years, median ECOG PS of 0, either ER positive or unknown, and had not received prior hormone therapy for metastatic disease. Overall objective response was observed in 9 (27%) patients. Complete response was observed in 2 cases and partial response in 7 patients. Median duration of response was 7 months (range 2-10). A higher response rate was observed in patients with predominantly soft tissue disease (38%) compared to patients with either dominant **bone** (18%) or visceral lesions (17%). Toxicity was mild and reversible: low grade fever in 30% of patients and flu-like symptoms in 9% of cases. It appears that IFN-B does not improve the efficacy of tamoxifen in an unselected population of metastatic breast cancer.

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L14 ANSWER 4 OF 29 MEDLINE
ACCESSION NUMBER: 94295168 MEDLINE
DOCUMENT NUMBER: 94295168 PubMed ID: 8023478
TITLE: [Therapeutic use of **interferon beta**].
Lecebne pouziti interferonu beta.
AUTHOR: Adam Z; Vorlicek J
CORPORATE SOURCE: II. interni klinika Fakultni nemocnice, Brno, Bohunice.
SOURCE: VNITRNI LEKARSTVI, **(1994 May)** 40 (5) 329-33.
Ref: 40
Journal code: XFY; 0413602. ISSN: 0042-773X.
PUB. COUNTRY: Czech Republic
Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: Czech
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199408
ENTRY DATE: Entered STN: 19940815
Last Updated on STN: 19940815
Entered Medline: 19940804

AB All types of interferon (alpha, beta, gamma) have a virostatic immunomodulating and antiproliferative effect. There are, however, quantitative differences between different interferons as regards the mentioned properties. **Interferon beta** has a marked antiviral action, and therefore it is used in a dose of 0.5 x 10(6) IU/kg in long-term infusions in life-endangering viral infections. **Interferon beta** differs from interferon alpha by a higher lipophilia and thus greater tissue affinity. It is therefore useful for local treatment. Local administration is used in severe infections of the anterior segment of the eye and in relapses of condyloma accuminatum and in warts. In oncology intra- and peritumourous administration is used which in the great majority of patients leads to a time-limited remission of metastases in soft tissues as well as in **bones**. Intrathecal **interferon beta** administration retarded in s minor group of patients the course of multiple sclerosis.

L19 ANSWER 63 OF 69 BIOSIS COPYRIGHT 2001 BIOSIS
ACCESSION NUMBER: 1989:182008 BIOSIS
TITLE: DECREASED CYTOKINE MESSENGER RNA LEVELS IN THE ELDERLY.
AUTHOR(S): GAUCHAT J-F; DEWECK A L; STADLER B M
CORPORATE SOURCE: INST. CLINICAL IMMUNOLOGY, INSELSPITAL, 3010 BERN, SWITZERLAND.
SOURCE: AGING IMMUNOL INFECT DIS, (1988) 1 (3), 191-204. CODEN: AIIDE9.
FILE SEGMENT: BA; OLD
LANGUAGE: English
AB Normal PBL stimulated by various agents were analysed for their levels of mRNAs coding for lymphokines (IL-2, IFN-.gamma., GM-CSF, IL-1.beta., IL-6) and surface receptors (IL-2R, CD2). An age-related decline of lymphokine mRNA levels was observed between two age groups of normal blood donors. The group of young donors ranged between 20-34 years and the elderly between 62-82 years. Using a biological assay to determine IL-2, no statistically significant alterations were observed between the two groups in contrast to the results obtained using the hybridization technique. Interestingly, reduced mRNA levels were also observed for "monokines" (IL-1, GM-CSF, IL-6), suggesting that lymphokine production in general is decreased in elderly individuals.

L19 ANSWER 64 OF 69 BIOSIS COPYRIGHT 2001 BIOSIS

L19 ANSWER 38 OF 69 BIOSIS COPYRIGHT 2001 BIOSIS
ACCESSION NUMBER: 1992:348962 BIOSIS
DOCUMENT NUMBER: BA94:41187
TITLE: DENGUE VIRUS INFECTION OF HUMAN SKIN FIBROBLASTS IN-VITRO PRODUCTION OF IFN-BETA IL-6 AND GM-CSF.
AUTHOR(S): KURANE I; JANUS J; ENNIS F A
CORPORATE SOURCE: DIV. INFECT. DIS. IMMUNOL., DEP. MED., UNIV. MASS. MED. CENT., WORCESTER, MASS. 01655, USA.
SOURCE: ARCH VIROL, (1992) 124 (1-2), 21-30.
CODEN: ARVIDF. ISSN: 0304-8608.
FILE SEGMENT: BA; OLD
LANGUAGE: English
AB Dengue virus is transmitted to humans by the bite of infected mosquitos. In our efforts to understand the pathogenesis of dengue virus infection, we examined whether skin fibroblasts can be infected in vitro with dengue viruses. Fibroblasts could be infected with dengue viruses, yellow fever virus and West Nile virus. Dengue virus antigen-positive cells were detected as early as 4 h and the percentage of dengue virus antigen-positive cells reached maximum levels by 24 h after infection. High titers of infectious dengue virus were also detected in the culture supernatants at 20 h after infection. Dengue virus-infected fibroblasts produced interferon-.beta. (IFN-.beta.), and the IFN-.beta. protected uninfected fibroblasts from dengue virus infection. Dengue virus-infected fibroblasts also produced interleukin 6 (IL-6) and granulocyte macrophage colony stimulation factor (GM-CSF). These results suggest that skin fibroblasts may be one of the cell types which first support dengue virus and other flavivirus infections in vivo after introduction by the bite of infected mosquito, and that production of IFN-.beta., IL-6, and GM-CSF by these virus-infected fibroblasts may be important host immune responses to control flavivirus infections.

L19 ANSWER 39 OF 69 BIOSIS COPYRIGHT 2001 BIOSIS

L16 ANSWER 111 OF 120 BIOSIS COPYRIGHT 2001 BIOSIS
ACCESSION NUMBER: 1989:182008 BIOSIS
TITLE: DECREASED CYTOKINE MESSENGER RNA LEVELS IN THE ELDERLY.
AUTHOR(S): GAUCHAT J-F; DEWECK A L; STADLER B M
CORPORATE SOURCE: INST. CLINICAL IMMUNOLOGY, INSELSPITAL, 3010 BERN, SWITZERLAND.
SOURCE: AGING IMMUNOL INFECT DIS, (1988) 1 (3), 191-204. CODEN: AIIDE9.
FILE SEGMENT: BA; OLD
LANGUAGE: English

L16 ANSWER 112 OF 120 MEDLINE DUPLICATE 47

L23 ANSWER 3 OF 196 MEDLINE DUPLICATE 3
ACCESSION NUMBER: 95224058 MEDLINE
DOCUMENT NUMBER: 95224058
TITLE: Bidirectional regulation of **osteoclast** function by nitric oxide synthase isoforms.
AUTHOR: Brandi M L; Hukkanen M; Umeda T; Moradi-Bidhendi N; Bianchi S; Gross S S; Polak J M; MacIntyre I
CORPORATE SOURCE: Department of Clinical Physiopathology, University of Florence Medical School, Italy.
SOURCE: PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, **(1995 Mar 28)** 92 (7) 2954-8.
Journal code: PV3. ISSN: 0027-8424.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals; Cancer Journals
ENTRY MONTH: 199507

AB Nitric oxide (NO) produces rapid **osteoclast** detachment and contraction in vitro, and this effect is accompanied by a profound inhibition of bone resorption. Work by others has confirmed these findings in vivo: inhibition of NO synthase [NOS; L-arginine, NADPH: oxygen oxidoreductase (NO-forming), EC 1.14.13.39] in normal rats is followed by increased bone resorption reflected by a marked loss in bone mineral density. In our present study, immunocytochemistry and Northern blotting show the presence of the constitutive calcium-sensitive NOS isoform (cNOS) in normal rat **osteoclasts** and in the human preosteoclast cell line (FLG 29.1). The inducible NOS isoform (iNOS) was also clearly demonstrable in the rat cells especially after treatment with **gamma interferon** (IFN-gamma) and bacterial wall products [lipopolysaccharide (LPS)], while a basal level of transcript was detected in the untreated human preosteoclast line. However NADPH-diaphorase activity was intense only in neonatal rat **osteoclasts** attached to bone, perhaps reflecting either enhancement of cNOS activity by calcium or increased amounts of the inducible isoform in activated **osteoclasts** in situ compared with isolated neonatal rat **osteoclasts**. These actively resorb devitalized bone but the untreated cells contain relatively low levels of NOS; they are extremely sensitive to inhibition by NO. The iNOS inhibitor aminoguanidine markedly enhances in vitro resorption by activated NOS-rich chick **osteoclasts** and by normal rat **osteoclasts** treated with LPS or IFN-gamma. In contrast, the nonselective NOS inhibitor NG-monomethyl-L-arginine inhibits resorption by untreated neonatal rat **osteoclasts**. Thus, **osteoclast** function may require intermittent calcium-stimulated increases in NO production by cNOS against a basal inhibitory background activity of the iNOS isoform. However, bone resorption depends on precursor replication and on the activity of the mature cells, and we found that the NO donor 3-morpholinosydnonimine (SIN-1) (50 microM) profoundly depressed replication in the human preosteoclast line. Taken together, these results strongly suggest that NO maintains a central control of bone resorption in both avian and mammalian

species by exerting a powerful tonic restraint of **osteoclast** numbers and activity. The presence of NOS in human cells implies a similar function in man and that conventional views of calcium homoeostasis and skeletal metabolism will need substantial revision. Since NO also influences behavior of the **osteoblast**, the bone-forming cell, in vitro, a similar effect in vivo might imply a general influence on bone remodeling.

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L31 ANSWER 3 OF 4 BIOSIS COPYRIGHT 2001 BIOSIS
ACCESSION NUMBER: 1993:44954 BIOSIS
DOCUMENT NUMBER: PREV199344021804
TITLE: Effect of **interferon beta**-ser on interleukin 6 production and on transcription of the nuclear factor IRF-1 in human myeloma cell lines.
AUTHOR(S): **Humpe, A. (1); Kiss, T.; Trumper, L. H.; Messner, H. A.**
CORPORATE SOURCE: (1) Dep. Med., Sect. Hematol. Oncol., Georg-August-University Goettingen, Robert-Koch-Str. 40, D-3400 Goettingen Germany
SOURCE: Annals of Hematology, (1992) Vol. 65, No. SUPPL., pp. A72.

Meeting Info.: Annual Congress of the German Society of Hematology and Oncology, Berlin, Germany, October 4-7, 1992. ANN HEMATOL
ISSN: 0939-5555.
DOCUMENT TYPE: Conference
LANGUAGE: English

L36 ANSWER 3 OF 6 MEDLINE
ACCESSION NUMBER: 87313146 MEDLINE
DOCUMENT NUMBER: 87313146
TITLE: [Beta interferon therapy in hairy cell leukemia]. IFN-beta-Therapie bei der Haarzelleukamie.
AUTHOR: von Wussow P; Duhlmann J; Grethlein T; Hirschmann W D; Hugl E; Koch O; Martin W R; Pees H W; Urbanitz W; Freund M
SOURCE: KLINISCHE WOCHENSCHRIFT, **(1987 Jul 15)** 65 (14) 688-90.
Journal code: KWH. ISSN: 0023-2173.
PUB. COUNTRY: GERMANY, WEST: Germany, Federal Republic of
(CLINICAL TRIAL)
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: German
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198712

AB Eleven patients with histologically proven hairy-cell leukemia were treated for 2 to 6 months with a natural **beta-interferon** (**beta**-IFN) preparation (3 X 4 million **units** week i.v.). Three of the eight evaluable patients experienced a partial response, two a minor response, and three no improvement. A reduction of the hairy-cell infiltration of the **bone** marrow was observed in one patient. Typical IFN side-effects with flu-like symptoms were noted. These results demonstrate that IFN-beta has some clinical efficacy in hairy-cell leukemia.

L14 ANSWER 19 OF 29 BIOSIS COPYRIGHT 2001 BIOSIS
ACCESSION NUMBER: 1993:429232 BIOSIS
DOCUMENT NUMBER: PREV199396083857
TITLE: Variation in lumbar spine and femoral neck **bone** mineral measured by dual energy X-ray absorption: A study of 329 normal women.
AUTHOR(S): Truscott, J. G. (1); Oldroyd, B. (1); Simpson, M. (1); Stewart, S. P. (1); Westmacott, C. F. (1); Milner, R. (1); Horsman, A.; Smith, M. A. (1)
CORPORATE SOURCE: (1) Cent. Bone and Body Composition Res., Inst. Phys. Sci.,
Dep. Clin. Med., Univ. Leeds, Wellcome Wing, Gen. Infirmary, Leeds LS1 3EX UK
SOURCE: British Journal of Radiology, (1993) Vol. 66, No. 786, pp. 514-521.
ISSN: 0007-1285.
DOCUMENT TYPE: Article
LANGUAGE: English
AB Reference ranges used in dual energy x-ray absorptiometry (DXA) have previously used piecewise linear fits to the whole data set for spine or femur **bone** mineral density (BMD) as a function of age. In a study of 329 Caucasian normal women we present a refinement to the normal range by fitting straight lines between quinquennial mean values of BMD for each site measured (lumbar spine, femoral neck and Ward's triangle). From the age of 40 years onwards the premenopausal women demonstrated minimal loss of BMD whereas postmenopausal women showed a rapid loss amounting to 27% in the lumbar spine, 27% in the femoral neck and 38% in the Ward's triangle region in the age range under examination. Comparison of quinquennial means for pre and postmenopausal women in age bands 45-49 years and 50-54 years shows that at these ages postmenopausal BMD is significantly lower than premenopausal BMD (P lt 0.05). This finding suggests that separate normal ranges should be used for pre and postmenopausal women. As reduction in the production of oestrogen is a major factor in postmenopausal **bone** loss and oestrogen function is related to years since menopause (YSM), a more logical way of displaying postmenopausal normal BMD ranges would be in terms of YSM rather than chronological age. Such data are given in this paper.

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